(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 May 2002 (02.05.2002)

PCT

(10) International Publication Number
WO 02/34259 A1

(51) International Patent Classification[7]: A61K 31/215, 31/12, A61P 9/00

(21) International Application Number: PCT/EP01/12425

(22) International Filing Date: 23 October 2001 (23.10.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PR 1038 26 October 2000 (26.10.2000) AU
PR 3424 28 February 2001 (28.02.2001) AU

(71) Applicant *(for all designated States except US)*: **FOURNIER LABORATORIES IRELAND LIMITED** [IE/IE]; Fourth Floor, 12 South Mall, Ireland Cork (IE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **WATTS, Gerald** [GB/AU]; 10 Stanley Street, Nedlands, Western Australia 6009 (AU). **PLAYFORD, David** [AU/AU]; 5 Frances St, Mt Lawley, Perth, Western Australia (AU).

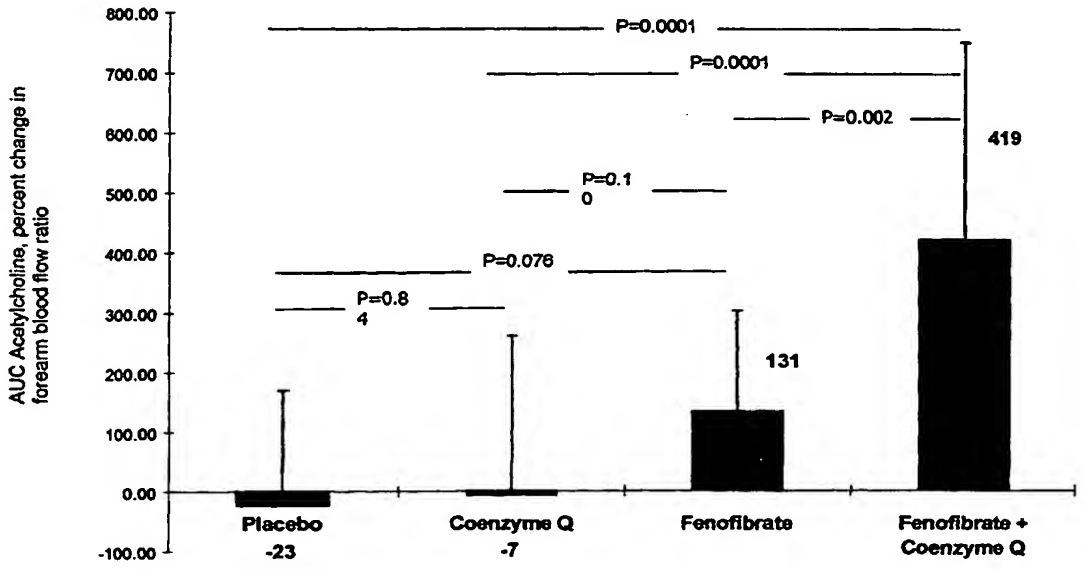
(74) Agents: **HUBERT, Philippe** et al.; Cabinet Beau De Loménie, 158 Rue de l'Université, F-75340 Paris Cedex 07 (FR).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: COMBINATION OF FENOFIBRATE AND COENZYME Q10 FOR THE TREATMENT OF ENDOTHELIAL DYSFUNCTION



(57) Abstract: The present invention relates to a combination of a peroxisome proliferator activated receptor (PPAR) activator and a benzoquinone and their use in treating and/or preventing disorders characterized by endothelial dysfunction, such as cardiovascular disease, strokes and myocardial infarction. According to a preferred embodiment of the invention the benzoquinone or precursor thereof is a ubiquinone or precursor thereof, more preferably, coenzyme Q_{10} or a precursor thereof, and the PPAR activator is a fibrate or a thiazolidinedione, more preferably fenofibrate.

WO 02/34259 A1

Published:
-- *with international search report*
·· *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

COMBINATION OF FENOFIBRATE AND COENZYME Q10 FOR THE TREATMENT OF ENDOTHELIAL DYSFUNCTION

FIELD OF THE INVENTION

The present invention relates to a combination of a peroxisome proliferator activated receptor (PPAR) activator and a benzoquinone and their use in treating and/or preventing disorders characterized by endothelial dysfunction, such as cardiovascular disease, strokes and myocardial infarction.

BACKGROUND TO THE INVENTION

The burden of cardiovascular disease is increasing in both developed and developing countries. This relates to an acceleration in the incidence of diabetes and obesity as well as to other cardiovascular risk factors, including hypercholesterolaemia, hypertension and smoking. All these conditions have in common a mechanism of vascular abnormality termed endothelial dysfunction (Rubanyi, 1993).

Nitric oxide (NO), a chemically unstable radical formed by enzymatic conversion of L-arginine in the presence of molecular oxygen, elicits relaxation of vascular smooth muscle cells. NO also counteracts platelet adhesion and aggregation. NO is released from endothelial cells by the action of acetylcholine (ACh). Failure of the vascular endothelium to elicit NO-mediated vasodilatation may be due to decreased formation of NO, increased degradation of NO and/or decreased biological sensitivity to NO. Irrespective of the mechanism this is referred to as endothelial dysfunction.

The vascular endothelium is also the site of formation of other vasodilator agents (e.g. prostacyclin, endothelium-derived hyperpolarizing factor), as well as vasoconstrictive factors (e.g. thromboxane A2, endothelin).

Endothelium dysfunction is highly relevant to vascular disease and occurs chiefly as a consequence of disturbances in the L-arginine/NO pathway.

Its occurrence in type 2 diabetes, for example, is extensively supported by both *in vitro* and *in vivo* studies (Cohen, 1993; Watts, 1998). Indeed, endothelial dysfunction may be the initiating event in the process of atherosclerosis eventually resulting in clinical coronary artery disease. In hypercholesterolemic subjects, impaired endothelium-dependent vasodilatation is evidenced before the development of atherosclerosis. In patients with type 2 diabetes endothelial function is abnormal even in the absence of elevated plasma LDL cholesterol concentration.

Endothelial dysfunction in diabetes may have implications not only for coronary artery disease, but also for peripheral vascular disease and retinopathy. Experimental and clinical studies support the concept that dyslipidemia (in particular increased circulatory concentrations of modified, small dense LDL), as well as hyperoxidative stress, are closely related to the development of endothelial dysfunction as a consequence of changes in the disposal of nitric oxide NO.

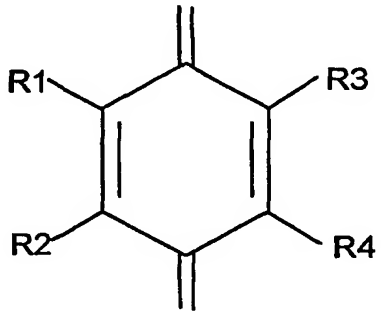
Oxidative stress represents a challenge to normal bodily functions. It may arise from an increase in exposure to free radicals/oxidants or may be a result of a decrease in anti-oxidant capacity. Oxidative stress is caused by reactive oxygen species which can be of both endogenous or exogenous origin. Endogenous sources of free radicals, such as the superoxide anion $O_2^{\bullet -}$, include endothelial cells, activated neutrophils and mitochondria. The term reactive oxygen species includes not only oxygen-centred radicals (e.g. superoxide and hydroxyl), but also non-radical derivatives of oxygen (H_2O_2), singulet oxygen and HOCl. In diabetes, as well as in myocardial infarction, stroke and inflammation, there is an increase in plasma levels of lipid hydroperoxides which are formed through a free radical-mediated mechanism from polyunsaturated fatty acids.

Accordingly, given the association between oxidative stress, endothelial dysfunction and a range of important disorders there is a need to provide an effective treatment for endothelial dysfunction caused by oxidative stress. In particular, type 2 diabetes is associated with a markedly increased risk of cardiovascular disease, its major complication.

Treatments have not been shown to be effective. There is a major need for new preventative and therapeutic strategies for cardiovascular disease.

DISCLOSURE OF THE INVENTION

Accordingly, the present invention provides a composition comprising a peroxisome proliferator activated receptor (PPAR) activator and a benzoquinone of formula I:



Formula I

in which :

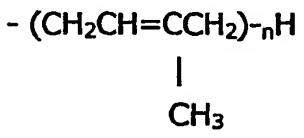
R1, R2 and R3 independently are :
- an alkyl group having 1 to 8 carbon atoms, or
- an alcoxy group having 1 to 8 carbon atoms;

R4 is :
- an hydrogen atom,
- an hydrocarbyl group having 1 to 60 carbon atoms,
- a OR5 radical,
- an SR6 radical,
- a N(R7)(R8) radical,
- a nitro group, or
- a carboxyl group;

R5, R6, R7 and R8 being independently :
- a hydrogen atom, or
- an alkyl group having 1 to 20 carbon atoms;

or a precursor thereof capable of being metabolized in the human or animal body to said benzoquinone;
or a pharmaceutically acceptable salt thereof.

In one preferred embodiment of the invention, said benzoquinone is of the formula (I) in which R_4 is an alkenyl group or a polyalkenyl group, preferably a group of formula :



in which n is an integer of from 1 to 12, preferably from 6 to 11.

Preferably the benzoquinone or precursor thereof is a ubiquinone or precursor thereof, more preferably, coenzyme Q_{10} or a precursor thereof.

Preferably, the PPAR activator is a PPARα or a PPARγ activator.

Preferably, the PPAR activator is a fibrate or a thiazolidinedione, more preferably fenofibrate.

The PPAR activator, such as fenofibrate, may be co-micronised with a solid surfactant. Preferably, the solid surfactant is sodium lauryl sulphate.

The present invention also provides a pharmaceutical composition comprising a composition of the invention together with a pharmaceutically acceptable carrier or diluent.

The present invention further provides a method of treating or preventing a disorder characterized by endothelial dysfunction in an individual which method comprises administering to said individual an effective amount of a peroxisome proliferator activated receptor (PPAR) activator and a benzoquinone of formula I or a precursor thereof capable of being metabolized in the human or animal body.

Typically, the disorder is selected from cardiovascular disease, hypertension, stroke, myocardial infarction, peripheral vascular disease, angina pectoris, cardiac failure, diastolic and/or systolic ventricular

dysfunction, macro and microangiopathy in patients with diabetes, and tissue damage related to ischemia or reperfusion.

The PPAR activator and benzoquinone may, for example, be administered separately, sequentially or concomitantly.

The present invention also provides a peroxisome proliferator activated receptor (PPAR) activator and a benzoquinone of formula I, or a precursor thereof capable of being metabolized in the human or animal body to said benzoquinone, for use in therapy.

Further, the present invention provides the use of a peroxisome proliferator activated receptor (PPAR) activator and a benzoquinone of formula I, or a precursor thereof capable of being metabolized in the human or animal body to said benzoquinone, in the manufacture of a medicament for use in treating a disorder characterized by endothelial dysfunction, as defined above.

Further still, the present invention provides a method for producing a composition of the invention which method comprises admixing said PPAR activator and benzoquinone.

The present invention also provides a method for producing a pharmaceutical composition of the invention which method comprises admixing said PPAR activator and benzoquinone with a pharmaceutically acceptable carrier or diluent.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing the acetylcholine percent change in forearm blood flow ratio as a result of the administration of coenzyme Q_{10} and/or fenofibrate; and

Figure 2 is a graph showing the sodium nitroprusside percent change in forearm blood flow ratio as a result of the administration of coenzyme Q_{10} and/or fenofibrate.

BEST MODE(S) FOR CARRYING OUT THE INVENTION

Throughout the specification, unless the context requires otherwise, the word "comprise" or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

PPAR activators

The peroxisome proliferator activated receptor (PPAR) (Issemann, 1990) is a member of the family of ligand-activated nuclear receptors including the estrogen receptor, the retinoic acid receptor (RXR) and the androgen receptor. These nuclear receptors are activated by the binding of a ligand, for example, estrogen, in the case of the estrogen receptor. The activation of the receptor enables the latter to then bind to a specific DNA sequence, termed the responsive element, in the promoter of a given gene leading thus to either an increase or in some cases a decrease in the transcription of the target gene.

PPAR is present as 2 main subtypes, PPARα and PPARγ. Both subtypes do not bind alone to the DNA promoter but must first dimerize with RXR. This heterodimer, composed of either PPARα and RXR or PPARγ and RXR then binds to a specific DNA sequence in the promoter, the peroxisome proliferator responsive element. The endogenous ligands for PPARα and PPARγ are not known but are thought to be long chain fatty acids and/or their metabolites (Keller, 1993). PPARα and PPARγ control the expression of genes involved in fatty acid and energy utilisation.

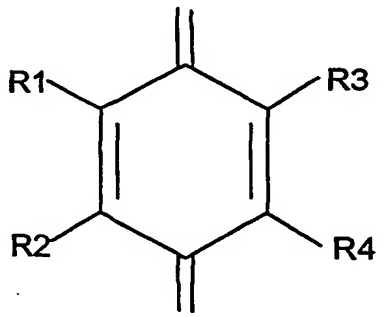
PPAR activators according to the present invention are activators of PPARα and PPARγ. A number of PPAR activators are known in the art including the fibrate and thiazolidinedione classes of drugs, for which fenofibrate and rosiglitazone, respectively, are well known examples. Activators of PPARα and PPARγ have overlapping as well as distinct pharmacological effects. In humans as well as in animal models, activation of PPARα with a fibrate, such as fenofibrate, or PPARγ with rosiglitazone leads to comparable lowering of serum triglycerides. Both PPARα and PPARγ are

expressed in muscle, while PPARα is preferentially expressed in hepatocytes and PPARγ in adipocytes. Fibrates mainly activate PPARα but bezafibrate has been shown to activate both PPARα and PPARγ. Similarly, rosiglitazone, an activator of PPARγ can also modify the expression of genes normally controlled by PPARα.

Preferred PPAR activators according to the present invention are agonists of PPARα activity. It is particularly preferred to use fibrates, such as fenofibrate. A further example of a member of the fibrate family is given in US 6028109.

Benzoquinones

Benzoquinones for use in the present invention are a benzoquinone of formula I:



Formula I

in which :

R1, R2 and R3 independently are :

- an alkyl group having 1 to 8 carbon atoms, or
- an alcoxy group having 1 to 8 carbon atoms;

R4 is :

- an hydrogen atom,
- an hydrocarbyl group having 1 to 60 carbon atoms,
- a OR5 radical,
- an SR6 radical,
- a N(R7)(R8) radical,

- a nitro group, or
- a carboxyl group; or

R5, R6, R7 and R8 being independently :

- a hydrogen atom,
- an alkyl group having 1 to 20 carbon atoms;

or a precursor thereof capable of being metabolized in the human or animal body to said benzoquinone;
or a pharmaceutically acceptable salt thereof.

In the description and the claims, the term "hydrocarbyl" is understood as meaning an organic group comprising at least C and H. If the hydrocarbyl group comprises more than one C, then those carbon atoms may be linked to each other directly by a single, double or triple bond, or indirectly by the intermediary of a suitable element or hetero atoms such as for example oxygen, sulfur or nitrogen atoms or a suitable group such as a carbonyl group.

The hydrocarbyl group may optionally comprise one or more suitable substituants. Examples of such substituants may include a halogen atom, an alkyl group having 1 to 8 carbon atoms, an alcoxy group having 1 to 8 carbon atoms, a nitro group, a bis alkyl group having 1 to 16 carbon atoms, a cyclic group having 1 to 16 carbon atoms, etc.

The hydrocarbyl group may be any one of an alkyl group, an alcoxy group, a polyalcoxy group, an aryl group, an acyl group, an alkenyl group, a polyalkenyl group, including combinations thereof (e.g. an arylalkyl group), which group may optionally contain one or more hetero atoms or one or more substituants on the chain or rings, as defined above.

The hydrocarbyl group is preferably a hydrocarbon group. Here the term "hydrocarbon" means any one of an alkyl group, an alkenyl group, an alkynyl group, which groups may be linear, branched or cyclic, or an aryl group, or combinations thereof (e.g. an arylalkyl group). The term hydrocarbon also includes those groups but wherein they have been optionally substituted. If the hydrocarbon is a branched structure having

substituent(s) thereon, then the substitution may be on either the hydrocarbon backbone or on the branch; alternatively the substitutions may be on the hydrocarbon backbone and on the branch.

In one preferred embodiment of the invention R1, R2 and R3 are each independently a lower alkyl group or a lower alkoxy group. The term "lower alkyl group" means a straight-chain or branched alkyl group having 1 to 8 carbon atoms, and examples thereof include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl (amyl), isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl and octyl groups. Among them, methyl, ethyl, propyl, isopropyl groups, etc., are preferable.

The term "lower alkoxy group" means a lower alkoxy group derived from the above-described lower alkyl group, such as methoxy, ethoxy and n-propoxy groups. Among them, a methoxy group is most preferred.

Preferably, R4 is an alkenyl group or a polyalkenyl group, i.e. a group having one or more double bonds in any portion of an alkyl group. R4 may comprise from 1 to 12, such as 6 to 11, preferably 9 or 10 repeats of an isoprenoid unit, such as 3-methyl-2-butene-1,4 diyl unit.

Preferably, R5, R6, R7 and R8 may each independently be H or C_1 to C_4 alkyl.

Compounds of the present invention may contain one or more asymmetric carbon atoms and/or one or more non-aromatic carbon-carbon double bonds and may therefore exist in two or more stereoisomeric forms. Thus, the present invention also provides individual stereoisomers of the compounds of the formula (I), as well as mixtures thereof, including compositions comprising the same.

Separation or diastereoisomers or *cis* and *trans* isomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or HPLC of a stereoisomeric mixture of a compound of the formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of the formula (I) may also be prepared from a corresponding optically pure intermediate or by resolution, such as by HPLC of a racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of a racemate with a suitable optically active acid or base.

Benzoquinones for use in the therapeutic methods of the present invention should have antioxidant properties, such as the ability to scavenge active oxygen species. In addition, benzoquinones for use in the therapeutic methods of the present invention will clearly need to be physiologically acceptable upon administration and not cause excessive side effects. For example, they should not be unduly toxic to patients. The toxicity of benzoquinones may be determined using a variety of methods known in the art including *in vitro* whole cell assays and LD_{50} animal tests.

US 5229385, for example, describes a range of benzoquinone derivatives having antioxidant properties which may be used therapeutically. EP-A-419905 also describes a number of benzoquinone derivatives suitable for therapeutic use.

It will be appreciated by the skilled person that since the benzoquinone coenzyme Q_{10} is synthesised *in vivo* from precursor molecules, it may be possible to administer a benzoquinone according to the present invention by means of a precursor that is capable of being converted to a benzoquinone by the same biosynthetic pathways that produce coenzyme Q_{10}. Typically, a precursor will be an immediate precursor, that is to say a molecule structuraly related to the benzoquinone and that needs to undergo only a small number of steps in the biosynthetic pathway before it is converted to a benzoquinone of formula I. It is generally preferred to administer precursors that are processed by parts of the coenzyme Q_{10} biosynthetic pathway which are unique to coenzyme Q. For example, chorismate is converted in the body to p-aminobutyric acid, p-

hydroxybenzoic acid, prephenate (which leads to phenylalanine and tyrosine) and is therefore not an immediate precursor since it supplies several pathways. By contrast, p-hydroxybenzoic acid is used only in the synthesis of ubiquinones and may be considered to be an immediate precursor.

The skilled person will appreciate that the reason for preferring immediate precursors is to avoid effects on other biosythetic pathways which may have a deleterious effect on the patient.

The skilled person will also appreciate that the benzoquinones according to the present invention are reduced in the human or animal body to a benzoquinol. Consequently, since it may be possible to administer benzoquinones in their reduced or oxidised state, references to benzoquinones throughout mean both the quinone and reduced quinol forms.

It is particularly preferred to use coenzyme Q, a naturally occurring agent which acts as an electron carrier in the mitochondrial electron transfer in the respiratory chain and which possesses several other functions. CoQ is synthesised from condensation of a benzoquinone ring and a hydrophobic side chain varying in size between species with elongation through a trans-prenyl transferase with multiple repeats of isopentenyl diphosphate units. In humans the side chain is composed of ten such repeats, that is the origin of its designation as CoQ_{10}.

In vivo the oxidized CoQ_{10} is converted to reduced $CoQ_{10}H_2$ or ubiquinol-10, a potent antioxidant in plasma, in lipoproteins and in tissues. It scavenges in plasma free radicals produced by lipid peroxidation. CoQ_{10} treatment has been previously demonstrated to be safe at doses up to 300 mg daily for the patient and in many countries different presentations are available over the counter. From previous evidence and as confirmed herein, CoQ_{10} plasma levels increase 3 to 4 fold after administration of 200 mg daily.

Administration

The amount of PPAR activator and benzoquinone or precursor thereof which is required to achieve the desired biological effect will, of course, depend on a number of factors, for example, the mode of administration and the precise clinical condition of the recipient. The following routes of administration and dosages described are intended only as a guide since a skilled practitioner will be able to determine readily the optimum route of administration and dosage for any particular patient and condition.

In general, the daily dose of each component will be in the range of 0.1 mg-100 mg/kg, typically 0.1-20 mg/kg. An intravenous dose may, for example, be in the range of 0.01 mg to 0.1 g/kg, typically 0.01 mg to 10 mg/kg, which may conveniently be administered as an infusion of from 0.1 µg to 1 mg, per minute. Infusion fluids suitable for this purpose may contain, for example, from 0.01 µg to 0.1 mg, per millilitre. Unit doses may contain, for example, from 0.1 µg to 1 g of each component. Thus ampoules for injection may contain, for example, from 0.1 µg to 0.1 g and orally administrable unit dose formulations, such as tablets or capsules, may contain, for example, from 0.1 mg to 1 g.

Preferably, the PPAR activator, particularly fenofibrate, is administered in an amount from about 50 to 450 mg daily and the benzoquinone or precursor thereof is administered in an amount from about 10 to 400 mg daily.

The PPAR activator and benzoquinone or precursor thereof may be administered as the compounds *per se*, but are preferably presented with an acceptable carrier or diluent in the form of a pharmaceutical composition. The carrier or diluent may be a solid or a liquid, or both, and is preferably formulated with the activator and benzoquinone as a unit-dose formulation, for example, a tablet, which may contain from 0.05% to 95% by weight of the active component.

The formulations include those suitable for oral, rectal, topical, buccal (e.g. sublingual) and parenteral (e.g. subcutaneous, intramuscular, intradermal or intravenous) administration.

Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges or tablets, each containing a predetermined amount of a PPAR activator and/or benzoquinone; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion.

In general, the formulations are prepared by uniformly and intimately admixing the active PPAR activator and/or benzoquinone with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet may be prepared by compressing or moulding a powder or granules of the PPAR activator and/or benzoquinone optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Moulded tablets may be made by moulding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising a PPAR activator and/or benzoquinone in a flavoured base, usually sucrose and acacia or tragacanth, and pastilles comprising the activator in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of a PPAR activator and/or benzoquinone, preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations may conveniently be prepared by admixing the activator with water and

rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 5% w/w of the activator and 0.1 to 5% w/w of the benzoquinone.

Formulations suitable for rectal administration are preferably presented as unit-dose suppositories. These may be prepared by admixing a PPAR activator and/or benzoquinone with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include vaseline, lanolin, polyethylene glycols, alcohols, and combinations of two or more thereof. The PPAR activator and/or benzoquinone are generally present at a concentration of from 0.1 to 15% w/w of the composition, for example, from 0.5 to 2%.

Preferably, the PPAR activator, such as fenofibrate is co-micronised with a solid surfactant (for example as described in AU-A-614577). A particularly preferred solid surfactant is sodium lauryl sulphate. Typically, the solid surfactant is used in an amount of from 1 to 4%.

The PPAR activator and benzoquinone may be administered separately, sequentially or simultaneously (such as when administered as a composition comprising both the PPAR activator and a benzoquinone).

In addition, it may also be desirable to administer, in addition to the PPAR activator and/or benzoquinone according to the present invention, further components, such as pharmaceutically active compounds that improve vascular condition. As specific examples, it may be desirable to administer aspirin, an antiotensin converting enzyme inhibitor and/oror a calcium channel blocker to the patients before or during treatment with the PPAR activator and benzoquinone.

Therapeutic uses

The mechanism of the improvement of vascular function with the combination of a PPAR activator such as fenofibrate and a benzoquinone such as CoQ_{10} is likely to be due to a direct effect on the vascular wall, independent to a large extent from the lipid lowering effects of the PPAR activator. This synergy could be explained at least in part by either an interaction with the formation, diffusion or action of endogenous NO or endothelium-derived hyperpolarizing factor remains possible. This is supported by the findings with acetylcholine (Ach), sodium nitroprusside (SNP) and the co-infusion of ACh + N^G -monomethyl-L-arginine (L-NMMA) in the setting of aspirin therapy. Pretreatment with aspirin also simulates best clinical practice of preventive medicine, given that aspirin has been shown to diminish cardiovascular events in patients with and without diabetes.

The improvement of endothelial dysfunction provided by the combination of a PPAR activator such as fenofibrate and a benzoquinone such as CoQ_{10} constitutes a new therapeutic approach which is easy to implement.

Beyond the synergy demonstrated herein with a combination of fenofibrate and coenzyme Q_{10}, similar effects could be obtained with a combination of other benzoquinone antioxidants (or their precursors) and other fibrates or PPAR activators which share with fenofibrate an effect on the expression of multiple genes involved in atherosclerosis, lipid metabolism and regulation of vascular wall function.

Thus, a combination of a PPAR activator and a benzoquinone may be used to treat or prevent disorders characterised by endothelial dysfunction, or an increased risk of endothelial dysfunctions. Examples of such disorders include cardiovascular events, cardiovascular disease, hypertension, stroke, myocardial infarction, peripheral vascular disease, angina pectoris, cardiac failure, diastolic and/or systolic ventricular dysfunction, macro and microangiopathy in patients with diabetes, and tissue damage related to ischemia and reperfusion. In particular, a combination of a PPAR activator and a benzoquinone may be used to treat patients with type 2 diabetes.

More specifically, the physiological effects associated with the administration of a combination of a PPAR activator and a benzoquinone may result in one or more of the following: improved vessel tone, reduced blood clotting, reduced platelet aggregation, reduced blood pressure and increased blood flow to the heart, reduced smooth muscle cell proliferation and inhibition of leucocyte chemotaxis.

Accordingly the present invention also provides a method of improving vessel tone, reducing blood clotting, reducing platelet aggregation, reducing blood pressure and increasing blood flow to the heart, reducing smooth muscle cell proliferation, and/or inhibiting leucocyte chemotaxis in a patient which method comprises administering to said patient an effective amount of a PPAR activator and a benzoquinone.

Vessel tone, platelet aggregation, blood pressure and blood flow, smooth cell proliferation and leucocyte chemotaxis may be measured using standard techniques prior to and during treatment to determine whether the PPAR activator and a benzoquinone are achieving the desired effect (see for example Furchgott, 1980; Garg, 1989; Radomski, 1987 and Moncada, 1991).

The present invention will now be described further by way of examples which are intended to be illustrative only and non-limiting.

EXAMPLES

Introduction

We have tested a combination of a peroxisome proliferator activated receptor (PPAR) activator, namely fenofibrate, and coenzyme Q_{10} for the treatment of vascular dysfunction in a randomized clinical trial involving patients with type 2 diabetes.

The results obtained demonstrate for the first time a synergism between a lipid lowering agent (the PPAR activator) and a radical scavenger in reducing vascular dysfunction. This synergistic effect was considered to be both statistically significant and clinically relevant. Support for the clinical

relevance of these finding is also provided by studies showing an association between endothelium dysfunction in peripheral arteries and endothelium dysfunction in the coronary arteries (Anderson, 1995; Sax, 1987) as well as longitudinal data showing that endothelial dysfunction predicts future coronary events (Suwaidi, 2000; Schachinger, 2000).

Compared with treatment with fenofibrate alone, the combination of fenofibrate with Coenzyme Q improves endothelial dysfunction and potentially reduces the progression of macro- and microvascular disease in type 2 diabetes. We would anticipate this to result in improvements with respect to coronary heart disease, peripheral vascular disease, ischemic stroke, renal disease and retinopathy in diabetes patients and by extension, to subjects with insulin resistance, hypertension and obesity.

Study design and methods:
Eighty dyslipidaemic patients with well controlled type 2 diabetes were randomised double-blind in a 2X2 factorial study to receive fenofibrate (F), CoQ_{10} (Q), fenofibrate and CoQ_{10} (FQ), or placebo (P) for 12 weeks. Male or female patients aged less than 70 years and without severe obesity (Body Mass Index below 35 kg/m^2) were included after a 6 week run-in period if they had Haemoglobin A1c below 9%, total cholesterol below 6.5 mmol/l and either triglyceride above 1.8 mmol/l or HDL cholesterol below 1 mmol/l. The two therapeutic agents alone or in combination were given each as 200 mg once daily. Capsules identical in appearance to each agent but containing placebo were given to maintain the double-blind nature of the study.

Evaluations of vascular function were carried out by bilateral venous occlusion plethysmography at weeks 0 and 12. These consisted of serial measurements of forearm blood flow before and after intra-brachial artery infusion of acetylcholine (ACh 7.5, 15 and 30 µg/min), sodium nitroprusside (SNP 1.5, 3 and 10 µg/min) and N^G-monomethyl-L-arginine (L-NMMA 4 µmol/l). These tests were performed after discontinuation of agents that might have changed vascular function such as ACE inhibitors and calcium channel blockers. Pretreatment with acetylsalicylic acid

(aspirin) (650 mg daily taken orally) was given for one week to block prostacyclin and thromboxane generation.

Plethysmography studies were performed during a 5 minute infusion of each agent, diluted in saline and infused at a rate of 1 mL/min into the brachial artery of the non-dominant arm via a thin plastic cannula Each infusion of vasoactive agents was preceded by a period of saline infusion. Bilateral forearm blood flow was measured simultaneously at 15 second intervals for the final two minutes of each 5 minute infusion period employing mercury-in-silastic strain gauges. During measurements hands were excluded from the circulation by inflation of wrist cuffs to 200 mmHg and venous occlusion was obtained by cyclical inflation of upper arm cuffs to 40 mmHg . Results were expressed as the area under the curve (AUC) of the percent increase in forearm blood flow ratio (infused arm versus control arm) to account for any systemic effect of these vasoactive drugs. The AUC provided integration over time of the dose response to the agent used. AUC for percent change in blood flow to ACh was *a priori* described as the primary efficacy criterion in this trial.

Statistical analyses were performed using 2 by 2 analysis of variance using SPSS package

Results:

Out of the 80 patients randomised, 77 completed the 12 week treatment period and paired blood flow data were available in 67; Three withdrawals occurred because of incidental medical conditions and one allergy to fenofibrate. 10 patients refused a second cannulation or could not be cannulated satisfactorily. The four groups were well matched in terms of baseline characteristics as shown on Table 1. Only 8 patients were on oral hypoglycaemic agents, none were on insulin. They presented with good diabetic control and with the typical characteristics of diabetic dyslipidemia.

Table 1: Patient characteristics: mean or distribution

	PP group	PQ group	PF group	FQ group
Gender (M/F)	14M/5F	18M/2F	14M/5F	14M/5F
Age (years)	55	53	54	52
BMI (kg/m^2)	31.0	29.9	30.0	30.6
BP (mm Hg)	137/78	128/76	131/74	132/77
HbA1c (%)	6.3	6.9	7.1	7.5
TC (mmol/l)	5.36	5.29	5.54	5.25
TG (mmol/l)	2.44	2.19	2.61	2.98
HDL-C (mmol/l)	1.02	0.95	0.95	0.93

Key : P = Placebo ; F = Fenofibrate ; Q = CoQ_{10}
BMI = body mass index; HbA1c = glycosylated hemoglobin A1c
TC = total cholesterol; TG = Triglyceride;
HDL-C = high density lipoprotein cholesterol

Table 2 shows the main study results where changes in treatment are presented in a 2X2 table consistent with the factorial study design.

Table 2: mean changes and their 95% confidence interval on treatment (Week 12 – Week 0) in acetylcholine AUC percent increase in forearm blood flow ratio

	P	**Q**	**F- v F+[95% CI]**
P	-23%[-143% to 95%]	-7%[-119% to 105%]	-15% [-97%to 66%]
F	131%[8% to 253%]	419%[287% to 550%]	275% [185%to 365%]
Q- v Q+	53% [-31% to 138%]	206% [119%to 192%]	

Key : P = Placebo ; F = Fenofibrate ; Q = CoQ_{10}
Analysis of variance Interaction p= 0.029, F effect p= 0.0001, Q effect p= 0.015

The combined effect of fenofibrate and CoQ_{10} treatment led to a 419% increase in forearm blood flow ratio, fenofibrate alone to a 131% increase while there was no change with CoQ_{10} alone or placebo. Thus, there was a clear synergism between fenofibrate and CoQ_{10} as evidenced by a significant interaction effect (p=0.029). Changes versus baseline were significant for the fenofibrate alone and the fenofibrate +CoQ_{10} groups but when the 4 groups were compared with each other only the combination treatment was significantly different from the 3 other groups (see figure 1)

When the vasodilatory response to ACh was reduced by co-infusion of L-NMMA similar results with a synergism between fenofibrate and coenzyme Q_{10} were observed (see Table 3).

Table 3: mean changes and their 95% confidence interval on treatment (Week 12 – Week 0) in acetylcholine percent increase in forearm blood flow ratio with co-infusion of L-NMMA

	P	Q	F- v F+[95% CI]
P	58%[-2% to 118%]	-21%[-76% to 33%]	18% [-22% to 59%]
F	47%[-10% to 47%]	118%[53% to 183%]	83% [39%to 126%]
Q- v Q+	53% [11% to 94%]	48% [6% to 90%]	

Key : P = Placebo ; F = Fenofibrate ; Q = CoQ_{10}
Analysis of variance Interaction p= 0.015, F effect p= 0.034, Q effect p= 0.884

Table 4 Mean changes and their 95% confidence interval on treatment (Week 12- week 0) in sodium nitroprusside AUC percent increase in forearm blood flow ratio (see Figure 2)

	P	Q	F- v F+[95% CI]
P	-240%[-632% to 152%]	50%[-641% to 740%]	-95%[-503% to 313%]
F	-11%[-521% to 500%]	1594%[728% to 2461%]	792% [352%to 1232%]
Q- v Q+	-126% [-841% to 361%]	822% [399% to 1245%]	

Key : P = Placebo ; F = Fenofibrate ; Q = CoQ_{10}
Analysis of variance Interaction p= 0.032, F effect p= 0.004, Q effect p= 0.002

These improvements in vascular endothelium function were not explained by any interaction between fenofibrate and CoQ_{10} on the lipid modifying

properties of fenofibrate; an increase in HDL-cholesterol, a decrease in total cholesterol, LDL-cholesterol, triglyceride or fibrinogen. Furthermore plasma levels of CoQ_{10} after treatment did not differ between the CoQ_{10} alone and the combination groups. There was no change in diabetes control or blood pressure measurements with the combination of fenofibrate and CoQ_{10}. CoQ_{10} alone had no lipid lowering effects.

All publications mentioned in the above specification are herein incorporated by reference.

Various modifications and variations of the described methods and system of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are apparent to those skilled in molecular biology or related fields are intended to be within the scope of the invention.

References

ANDERSON TJ, UEHATA A, GERHARD MD, et al. Close relationship of endothelial function in the human coronary and peripheral circulation. J Am Coll Cardiol 1995;26:1235-41.

COHEN RA. Dysfunction of vascular endothelium in diabetes mellitus. Circulation 1993;97(Suppl V):V67-V76.

ISSEMANN I, GREEN S. Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. Nature 1990;347:645-50.

FURCHGOTT RF, ZAWADZKI JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980: 299:373-376.

GARG UC, HASSID A. Nitric oxide-generating vasodilators and 8-bromo-cyclic guanosine monophosphate inhibit mitogenesis and proliferation of cultured rat vascular smooth muscle cells. J Clin Invest 1989: 83:1774-1777.

KELLER H., DREYER C., MEDIN J., MAHFOUDI A., OZATO K., WAHLI W. Fatty acids and retinoids control lipid metabolism through activation of peroxisome proliferator-activated receptor-retinoid X receptor heterodimers. Proc. Natl. Acad. Sci. 1993;USA 90:2160-64.

MONCADA S, PALMER RM, HIGGS EA. Nitric oxide: physiology, pathophysiology, and pharmacology. Pharmacol.Rev 1991: 43:109-142.

RADOMSKI MW, PALMER RM, MONCADA S. Endogenous nitric oxide inhibits human platelet adhesion to vascular endothelium. Lancet 1987: 2:1057:1058.

RUBANYI GM. The role of endothelium in cardiovascular homeostasis and diseases. J Cardiol Pharmacol 1993;22(suppl 4):51-514.

SAX FL, CANNON RO III, HANSON C, EPSTEIN SE. Impaired forearm vasodilator reseve in patients with microvascular angina. Evidence of a

generalized disorder of vascular function? N Engl J Med 1987;317:1366-70.

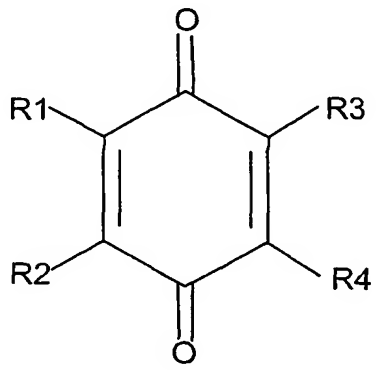
SCHACHINGER V, BRITTEN MB, ZEIHER AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation 2000;101:1899-1906.

SUWAIDI JS, HAMASAKI S, HIGANO ST, *et al.* Long term follow-up of patients with mild coronary artery disease and endothelial dysfunction. Circulation 2000;101:948-54.

WATTS GF, PLAYFORD DA. Dyslipoproteinemia and hyperoxidative stress in the pathogenesis of endothelial dysfunction in non-insulin dependent diabetes mellitus: an hypothesis Atherosclerosis 1998;141:17-30.

CLAIMS

1. A composition comprising a peroxisome proliferator activated receptor (PPAR) activator and a benzoquinone of formula (I):



Formula I;

in which :

R1, R2 and R3 independently are :
- an alkyl group having 1 to 8 carbon atoms, or
- an alcoxy group having 1 to 8 carbon atoms;

R4 is :
- an hydrogen atom,
- an hydrocarbyl group having 1 to 60 carbon atoms,
- a OR5 radical,
- an SR6 radical,
- a N(R7)(R8) radical,
- a nitro group, or
- a carboxyl group;

R5, R6, R7 and R8 being independently :
- a hydrogen atom, or
- an alkyl group having 1 to 20 carbon atoms;

or a precursor thereof capable of being metabolized in the human or animal body to said benzoquinone;
or a pharmaceutically acceptable salt thereof.

2. A composition according to claim 1 wherein, said benzoquinone is of the formula (I) in which R_4 is an alkenyl group or a polyalkenyl group, preferably a group of formula :

$$-(CH_2CH{=}\underset{\displaystyle CH_3}{\underset{|}{C}}CH_2)_{n}H$$

in which n is an integer of from 1 to 12, preferably from 6 to 11.

3. A composition according to claim 1 or 2 wherein the above mentioned benzoquinone or precursor thereof is a ubiquinone or precursor thereof, more preferably, coenzyme Q_{10} or a precursor thereof.

4. A composition according to any one of claims 1 to 3 wherein the above mentioned PPAR activator is a PPARα or a PPARγ activator.

5. A composition according to claim 4 wherein the above mentioned PPAR activator is a fibrate or a thiazolidinedione, more preferably fenofibrate.

6. A composition according to claim 5 wherein the above mentioned PPAR activator, such as fenofibrate, is co-micronised with a solid surfactant.

7. A composition according to claim 6 wherein the above mentioned solid surfactant is sodium lauryl sulphate.

8. A pharmaceutical composition comprising a composition according to any one of claims 1 to 7, together with a pharmaceutically acceptable carrier or diluent.

9. A method for producing a pharmaceutical composition as claimed in claim 8, which comprises admixing said PPAR activator and benzoquinone with a pharmaceutically acceptable carrier or diluent.

10. A composition comprising a peroxisome proliferator activated receptor (PPAR) activator and a benzoquinone of formula I as defined in any of claims 1 to 7, or a precursor thereof capable of being metabolized in the human or animal body to said benzoquinone, for use in therapy.

11. The use of a composition as claimed in any of claims 1 to 7 for the manufacture of a medicament for use in treating a disorder characterized by endothelial dysfunction.

12. The use according to claim 11 wherein the above mentioned disorder is selected from the group consisting of cardiovascular disease, hypertension, stroke, myocardial infarction, peripheral vascular disease, angina pectoris, cardiac failure, diastolic and/or systolic ventricular dysfunction, macro and microangiopathy in patients with diabetes, and tissue damage related to ischemica or reperfusion.

13. The use according to claim 11 or 12 wherein the above mentioned medicament is in a form adapted for an administration of said peroxisome proliferator activated receptor (PPAR) activator and benzoquinone in a separate, sequential or concomitant manner.

Figure 1

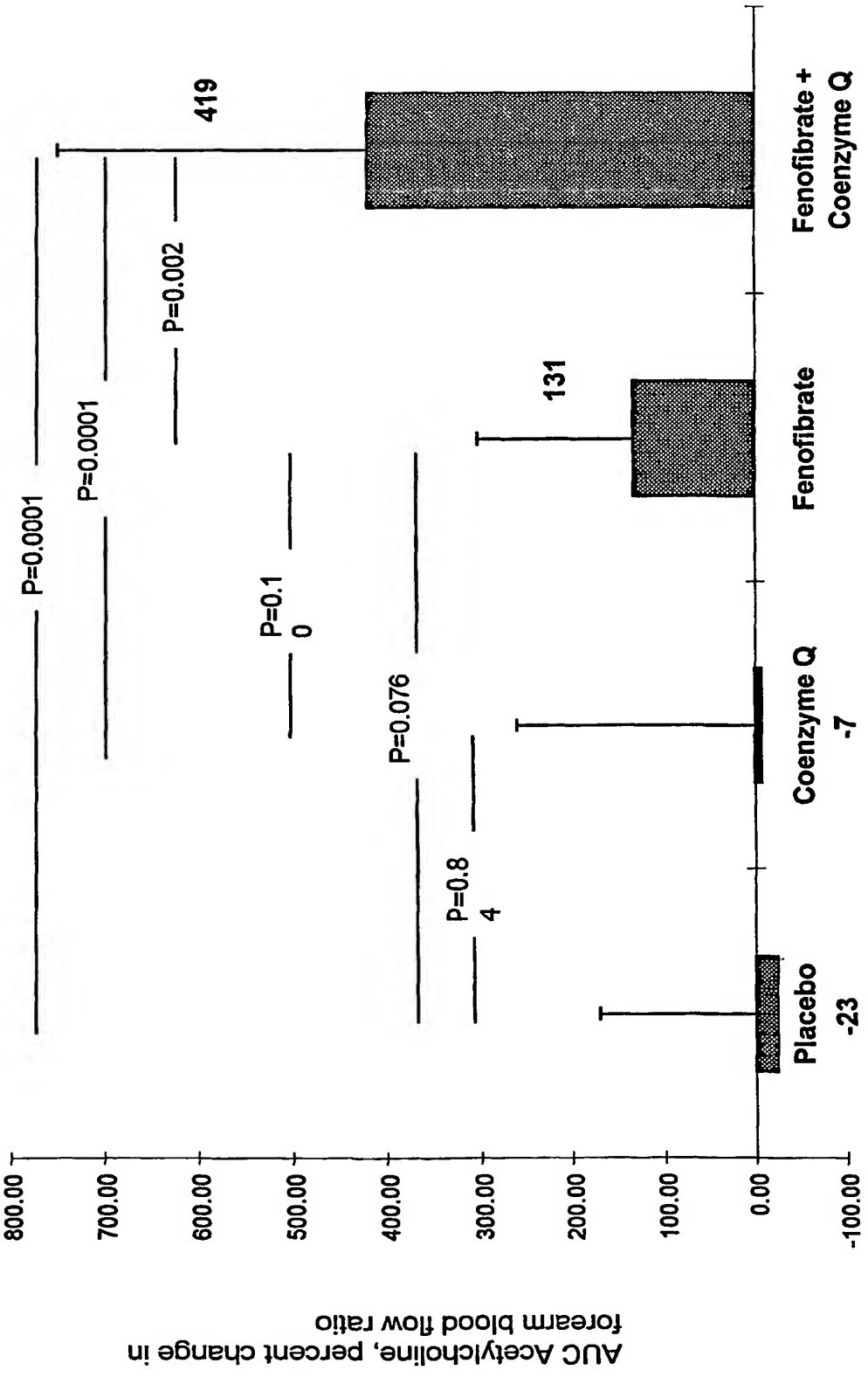
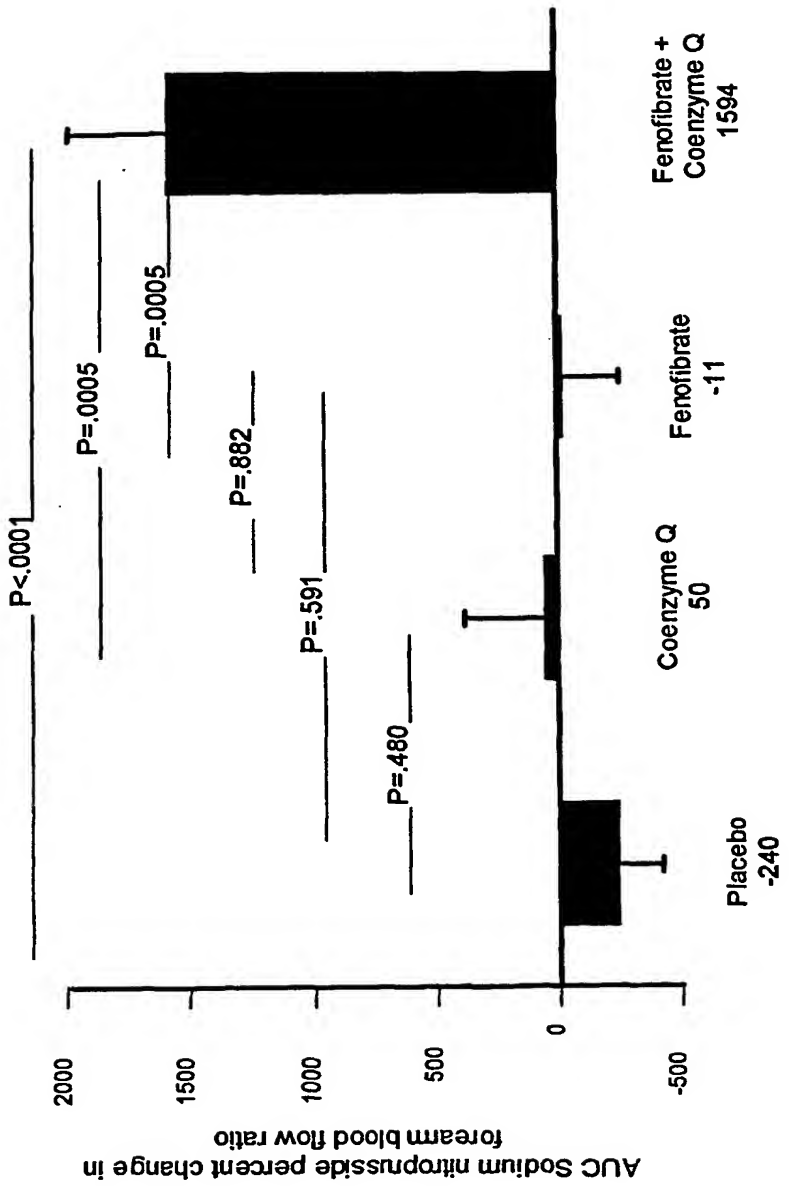


Figure 2



INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/12425

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/215 A61K31/12 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, CHEM ABS Data, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BELICHARD P ET AL: "Effect of a long-term treatment with lovastatin or fenofibrate on hepatic and cardiac ubiquinone levels in cardiomyopathic hamster." BIOCHIMICA ET BIOPHYSICA ACTA, (1993 JUL 21) 1169 (1) 98-102., XP001019683	1-3,5-13
Y	see discussion page 102, paragraph 3	1-13
A	WO 97 28149 A (AUWERX JOHAN ;BERGER JOEL P (US); MERCK & CO INC (US); MOLLER DAVI) 7 August 1997 (1997-08-07) page 15, line 28-30; claims 14,27,38.49	1-13
Y	US 5 880 148 A (EDGAR ALAN DUNLAP ET AL) 9 March 1999 (1999-03-09) abstract; claims 1,9	1-13

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the International filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 April 2002	16/04/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Gonzalez Ramon, N

Form PCT/ISA/210 (second sheet) (July 1992)

INTER[redacted]TIONAL SEARCH REPORT

[redacted]ional Application No
P[redacted]/EP 01/12425

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 034 791 A (KARSANOV NIKOLAI VASILIEVICH) 13 September 2000 (2000-09-13) abstract; table 1	1-13

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: partially 1-4,8-13

Present claims 1-4,8-13 relate to a compound/composition defined by reference to a desirable characteristic or property, namely: "peroxisome proliferator activated receptor (PPAR) activator" , " a precursor capable of beeing metabolized in the human or animal body to said benzoquinone" The claims cover all compounds/compositions having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Moreover claims 1-4,8-13 relate to an extremely large number of possible compounds. In fact, the claims contain so many options and possible permutations that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds specifically mentioned in the examples and in claims 3,5 and those encompassed by formula I with due regard to the general idea underlying the present application

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 01/12425

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9728149	A	07-08-1997	AU	1856997 A	22-08-1997
			AU	721452 B2	06-07-2000
			AU	2115997 A	22-08-1997
			CA	2245529 A1	07-08-1997
			EP	0888278 A1	07-01-1999
			JP	2002503202 T	29-01-2002
			WO	9728115 A1	07-08-1997
			WO	9728149 A1	07-08-1997
			AU	712607 B2	11-11-1999
			AU	1858197 A	22-08-1997
			CA	2244831 A1	07-08-1997
			EP	1011651 A1	28-06-2000
			JP	2000504021 T	04-04-2000
			WO	9727847 A1	07-08-1997
			AU	719146 B2	04-05-2000
			AU	2250797 A	22-08-1997
			CA	2245524 A1	07-08-1997
			EP	0904079 A1	31-03-1999
			WO	9727857 A1	07-08-1997
			AU	708055 B2	29-07-1999
			AU	1856397 A	22-08-1997
			EP	0882029 A1	09-12-1998
			JP	2002503203 T	29-01-2002
			WO	9728137 A1	07-08-1997
			US	5859051 A	12-01-1999
			US	6090836 A	18-07-2000
			ZA	9700824 A	30-10-1998
			US	6020382 A	01-02-2000
			US	5847008 A	08-12-1998
			AU	719663 B2	11-05-2000
			AU	5615298 A	17-07-1998
			EP	0948327 A1	13-10-1999
			JP	2001511767 T	14-08-2001
			WO	9827974 A1	02-07-1998
			US	6160000 A	12-12-2000
			US	6090839 A	18-07-2000
US 5880148	A	09-03-1999	FR	2730231 A1	09-08-1996
			AT	194078 T	15-07-2000
			DE	69608974 D1	03-08-2000
			DE	69608974 T2	08-02-2001
			DK	724877 T3	16-10-2000
			EP	0724877 A1	07-08-1996
			ES	2148694 T3	16-10-2000
			GR	3034147 T3	30-11-2000
			JP	8253416 A	01-10-1996
			PT	724877 T	29-12-2000
EP 1034791	A	13-09-2000	WO	9927952 A1	10-06-1999
			AU	6126098 A	16-06-1999
			EP	1034791 A1	13-09-2000